

Application No.: 09/863,982  
Filing Date: 21 May 2001

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# EXHIBIT A



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	Group Art Unit: 1209
Steven C. Quay	)	Examiner: S. Kumar
Serial No. 08/380,085	)	
Filed: JANUARY 30, 1995	)	<u>AMENDMENT</u>
For: PERSISTENT GASEOUS BUBBLES	)	2001 Ferry Building
AS ULTRASOUND CONTRAST	)	San Francisco, CA 94111
MEDIA	)	(415) 433-4150
		Docket No. SNUS 121

Honorable Commissioner of Patents  
and Trademarks  
Washington, D.C. 20231

Sir:

In response to the Official Action mailed  
June 26, 1995, please amend the above-identified  
application as follows.

AMENDMENTS

Apparently the supplemental preliminary  
amendment which was filed by applicant (by facsimile)  
on April 7, 1995 did not reach the file, at least at  
the time the pending office action was issued. In  
case that amendment has now appeared in the file and  
for the avoidance of confusion, please cancel (do not  
enter) the supplemental preliminary amendment faxed  
to Examiner Kumar on April 7, 1995.

IN THE CLAIMS

Please amend the claims in this application as  
follows:

Cancel claims 3-12 and 15-33 and add new claims  
34-46 as follows:

P 30112 02/01/96 08380085

12-1420 030 102

15A 00001

--34. Contrast media for ultrasound imaging comprising gaseous dodecafluoropentane.

*p* <sup>2</sup>35. The contrast <sup>media</sup> agent of claim <sup>1</sup>34 wherein a portion of said dodecafluoropentane is present as microbubbles suspended in a carrier.

*D* <sup>3</sup>36. The contrast <sup>media</sup> agent of claim <sup>2</sup>35 wherein said carrier is an aqueous liquid.

*C* *p* <sup>4</sup>37. The contrast <sup>media</sup> agent of claim <sup>3</sup>36 wherein a portion of said microbubbles are less than 8 microns in diameter.

<sup>5</sup>38. A biocompatible ultrasound contrast agent containing gas-filled liposomes, the improvement comprising including dodecafluoropentane in said gas.

<sup>6</sup>39. A biocompatible ultrasound contrast agent containing a suspension of encapsulated air-filled microspheres, the improvement comprising replacing all or a portion of the air with dodecafluoropentane.

<sup>7</sup>40. A biocompatible ultrasound contrast agent containing a suspension of crystals in a saccharide diluent, the improvement comprising providing gaseous dodecafluoropentane in said diluent.

<sup>8</sup>41. A biocompatible ultrasound contrast agent containing an emulsion of highly fluorinated organic compounds, the improvement comprising providing gaseous dodecafluoropentane in said emulsion.

<sup>9</sup>42. A biocompatible ultrasound contrast agent containing an air-filled microbubble suspension, the

improvement comprising providing dodecafluoropentane gas within the microbubbles of said suspension.

<sup>10</sup>  
43. Contrast media for ultrasound imaging comprising gaseous perfluorohexane.

<sup>11</sup>  
44. The contrast agent of claim <sup>10</sup>43 wherein a portion of said perfluorohexane is present as microbubbles suspended in a carrier.

<sup>12</sup>  
45. The contrast agent of claim <sup>11</sup>44 wherein said carrier is an aqueous liquid.

<sup>13</sup>  
46. The contrast agent of claim <sup>12</sup>45 wherein a portion of said microbubbles are less than 8 microns in diameter.--

## REMARKS

Reconsideration is respectfully requested. As a preliminary matter, and as stated above, Applicant requests cancellation of the Supplemental Preliminary Amendment filed by facsimile on April 7, 1995 (apparently not received by Examiner Kumar).

Entry of the present amendment and reconsideration of the pending rejections are respectfully requested.

Pending Objections and RejectionsA. 35 U.S.C. § 112

The Examiner has objected to the specification and rejected claims 3-12 and 15-33 under 35 U.S.C. § 112, first paragraph for allegedly failing to

provide an enabling disclosure. The rejection is obviated by the cancellation of these claims.

B. Obviousness-Type Double Patenting

The Examiner has rejected claim 33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 5,393,524. This rejection is avoided by the cancellation of claim 33.

All pending claims stand provisionally rejected under the doctrine of obviousness-type double patenting. This rejection is avoided by the cancellation of claims 3-12 and 15-33.

C. Support for Applicant's Added Claims

Applicant adds new claims 34-42, directed to ultrasound contrast media including dodecafluoropentane, some of which claims are drafted in "Jepson" format to highlight the improvement made by applicant.

Gaseous dodecafluoropentane as a contrast agent is disclosed in the specification in numerous places, see specifically example 6.

Jepson style claims 38-42 are supported in the specification where such prior art carrier technologies are described (beginning at p. 13 "The Materials Presently Used As Contrast Agents": claim 38 (liposomes) see page 15, last sentence, claim 39 ("encapsulated air-filled microspheres") see page 12, line 20 through page 13, line 10; claim 40 (crystals in saccharide diluent) page 15, first paragraph; claim 41, ("emulsion of highly fluorinated organic compounds") page 15, lines 19-20; and claim 42 ("an air-filled microbubble suspension") page 30, line 9-20, referring to US 4,832,941.

With respect to claims 43-46 ("gaseous perfluorohexane"), see example 6, which discloses the

very high "Q" value of perfluorohexane and compares the difference in contrast between gaseous perfluoropentane (very good) and liquid perfluorohexane (poor). As is explained, both a high Q value and a gaseous state are required to be a desired agent within the present invention, thus, claims 43-46 are limited to gaseous perfluorohexane.

D. Obviousness

The Examiner has rejected claims 3-12 and 15-33 under 35 U.S.C. § 103 as allegedly being unpatentable over the combined teachings of Ophir et al. (article 1989), Cerny et al. '656, Unger '319 and Davis et al '363. These claims have been cancelled.

Nevertheless, applicant provides an explanation of the patentability of the newly added claims over these references and others as follows.

Applicant acknowledges that small microbubbles of air and its constituent gases are disclosed in the prior art (e.g. 10 microns). Applicant also acknowledges that liquid fluorocarbon containing emulsions are disclosed for use as ultrasound contrast agents in the prior art. What the art does not show is the use of gaseous dodecafluoropentane or gaseous perfluorohexane recited in the pending claims for use in ultrasound contrast.

The Examiner argues that the Unger and Davis patents show that "fluoro containing chemicals" are known from this art. The Examiner is correct that Unger discloses fluorocarbons. However, Unger fails to disclose or suggest the use of gaseous dodecafluoropentane or gaseous perfluorohexane as part of any ultrasound contrast media.

There is simply no disclosure of these inventions in Unger. Rather, Unger discloses the use of a liquid in liquid fluorocarbon containing

emulsion (which was old and well known in the art, including for ultrasound contrast) for a new use: therapeutic heating by use of ultrasonic energy.

Likewise Davis neither teaches nor suggests the presently claimed inventions. Davis, et al. '363 teach that a liquid perfluorodecalin containing oil in water emulsion can be stabilized by the addition of selected liquid fluorocarbon compound that has a higher boiling point than perfluorodecalin. Davis et. al. disclose the prior art applicant has acknowledged above: the use of perfluorocarbon liquid-in-liquid emulsions as oxygen carriers and contrast agents. But Davis et. al. nowhere disclose gaseous dodecafluoropentane or gaseous perfluorohexane.

Thus, the cited art completely fails to suggest the claimed combinations.

Applicant readily acknowledges that there are teachings of using certain gases for ultrasound contrast with various carriers in the art. For example, see Glajch, et al. (U.S. patent 5,147,631 at Col. 6, lines 60-63), Berwing, et al. (U.S. Patent No. 4,832,941 - Col. 3, lines 50-53), Hilmann, et al. (U.S. Patent 4,466,442 at Col. 4, lines 40-44), AU 89-40652 (WO 90/019520) (See page 19), and Swanson, et al. "Pharmaceuticals in Medical Imaging" (page 685, col. 2, line 5) (see Applicant's IDS filed June 21, 1995 - the Examiner is requested to acknowledge receipt of the same). However, these references provide no guidance to the skilled artisan with respect to the selection of either gaseous dodecafluoropentane or perfluorohexane.

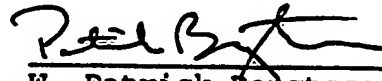
CONCLUSION

In light of the amendments and the arguments set forth above, Applicant respectfully requests early and favorable action. Should the Examiner have any questions he is encouraged to telephone the undersigned at 415-773-3129.


Respectfully Submitted,  
LIMBACH & LIMBACH

Date: 12-22-95

By

  
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FACSIMILE CERTIFICATE	
Date of Deposit:	December 22, 1995
I hereby certify that this correspondence is, on the date shown below, being transmitted by facsimile to the Patent and Trademark office by using the following facsimile number: 703/305-4566	
LIMBACH & LIMBACH	
By:	
Name: Person Called:	Leslie Mills
Date:	December 22, 1995